Paper No. 32

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MARTIN J. EVANS,
ROBERT M. MOOR and
ELENA NOTARANNI

Appeal No. 1995-1977
Application 07/669,403

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-4, 8, 9, and 14. Claims 6 and 11-13 are pending but were withdrawn from consideration following a restriction under 35 U.S.C. § 121.

Claims 1 and 8 are representative of the subject matter on appeal, and read as follows:

1. Pluripotential embryonic stem cells isolated from an ungulate species blastocysts of embryos that develop by way of an embryonic disc.

8. A method of selecting and growing pluripotential embryonic stem cells according to claim 1, comprising the steps of:

growing blastocysts in tissue culture growth medium which includes both heat-inactivated new born calf serum and heat-inactivated fetal calf serum;

disaggregated the blastocysts either after spontaneous hatching or after mechanical removal of the zone pellucida;

growing stem cell colonies from the disaggregated cells in tissue culture growth medium;

selecting stem cell colonies by morphological characteristics; and

growing the selected stem cells in tissue culture growth medium;

wherein the morphologically selected cells are capable of culture in a tissue culture dish to exhibit the following morphological features:

a) they are round cells, tightly packed with large nuclei in relation to cytoplasm, and fairly prominent nucleoli;

b) they grow in tightly adherent colonies, and as the colonies get larger the cells tend to flatten out in the centre of the colony, with the colony having an outer rim of cells of the form described in a), and

c) on trypsinization of the such a colony it may be seen that the outer, less flattened cells of a larger colony or all the cells of a smaller colony without central flattening are readily disaggregated by trypsinization into small spherical cells which have a bright phase contrast appearance, and if observed after a short time of incubation at 37° show lobular pseudopodia.

The references relied on by the examiner are:

Piedrahita et al. (Piedrahita), "Isolation of Embryonic Stem Cell-like Colonies From Porcine Embryos," Theriogenology, Vol. 29, No. 1, p. 286 (1988).

Ware et al. (Ware), "Development of Embryonic Stem Cell Lines From Farm Animals," Biology of Reproduction, Vol. 38, p. 129 (1988).

Doetschman et al. (Doetschman), "Establishment of Hamster Blastocyst-Derived Embryonic Stem (ES)," Developmental Biology, Vol. 127, pp. 224-27 (1988).

Evans et al. (Evans), "Establishment in Culture of Pluripotential Cells From Mouse Embryos," Nature, Vol. 292, pp. 154-56 (1981).

Claims 1-4 and 14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by either Piedrahita or Ware. In the alternative, the same claims were rejected under 35 U.S.C. § 103 as being not patentably distinct from the teachings of the same references.

Claims 8 and 9 stand rejected under 35 U.S.C. § 103 over either of Ware or Doetschman, taken in view of Evans.

We affirm the rejection of claims 1-4 and 14 and reverse the rejection of claims 8 and 9.

BACKGROUND

Appellants' specification states that "[p]rocedures for the isolation of murine embryonic stem cell lines are now well established." Specification, page 7. The specification also discloses, however, that isolation of embryonic stem (ES)[1] cells from ungulates such as cattle or pigs was not a routine matter of

[1] In his declaration under 37 CFR § 1.132, inventor Martin J. Evans draws a distinction between "embryonic stem cells" and "ES cells." However, Dr. Evans cites no evidence to indicate that those of skill in the art recognize a distinction between these terms and the instant specification draws no distinction between these terms. We, therefore, treat the terms as synonymous.

applying the methods developed for murine cells to cells from other animals. See the specification, page 5: "it is unlikely that the methods as described for mouse and utilised for hamster will be directly applicable to other embryos." The prior art of record also notes that the mouse methods were not directly applicable to ungulate cells. See Ware: "[C]onditions described for ES isolation in mice have not been amenable among farm animals for the long-term rapid cell proliferation that is characteristic of ES cells."

Appellants' specification discloses a method of isolating embryonic stem cells from ungulate species. The application provides examples showing isolation of ES cells from cattle and pigs. Appellants claim isolated ungulate embryonic stem cells and the disclosed method of isolating such cells.

DISCUSSION

1. The rejection under § 102(b)

The examiner rejected claims 1-4 and 14, which are drawn to isolated embryonic stem cells, under 35 U.S.C. § 102(b) as being anticipated by either of Piedrahita or Ware.[2] Since we agree with the examiner that the claims are anticipated by Piedrahita, we will not further discuss Ware.

Piedrahita teaches isolation of porcine embryonic stem cells. Piedrahita states that one of the resulting cell lines (designated P3) was characterized by round cells having large nuclei and prominent nucleoli. As the examiner notes, these properties are also characteristic of the ungulate embryonic stem cells disclosed in the instant specification. See the specification at page 18: "stem

[2] Because we find that Piedrahita anticipates claims 1-4 and 14, we will not address the alternative rejection under 35 U.S.C. § 103.

cells have the following features: a) They are round cells, tightly packed with large nuclei in relation to cytoplasm, and fairly prominent nucleoli."

In addition, Piedrahita notes that the morphology of this cell line closely resembles mouse teratocarcinoma cells. The instant specification similarly states that the embryonic stem cells isolated by Appellants resemble teratocarcinoma cells in their appearance and form of growth. See the specification, page 23.

Thus, the porcine embryonic stem cells disclosed by Piedrahita share several of the morphological features disclosed by the instant specification as being characteristic of the claimed embryonic stem cells. In addition, none of the properties of the P3 cells disclosed by Piedrahita are incompatible with their being ungulate embryonic stem cells. We therefore agree with the examiner that the cited reference supports a prima facie finding of anticipation, and shifts the burden to Appellants to show that the prior art does not in fact disclose the claimed invention. See In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) ("[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not."); Ex parte Maizel, 27 USPQ2d 1662, 1667-68 (Bd. Pat. App. Int. 1992) ("When an examiner obtains a product which reasonably appears to fall within the scope of that which is claimed by a patent applicant, it is reasonable to shift the burden to the applicant to provide evidence showing that the product of the prior art does not fall within the scope of applicants' [sic] claims.").

In response to this rejection, Appellants argue that the claimed ungulate embryonic stem cells differ in at least four ways from the previously known

murine embryonic stem cells. First, the morphology of the ungulate embryonic stem cells differs from that of murine embryonic stem cells. Therefore, Appellants argue, a prior art reference to "stem-like" cells is actually evidence that the cells isolated were not embryonic stem cells. Second, the ungulate embryonic stem cells isolated by Appellants were slow-growing, in contrast to the fast-growing murine embryonic stem cells. Therefore, Appellants argue, a reference disclosing fast-growing ungulate embryonic stem cells does not disclose the claimed invention. Third, Appellants argue that the cells must be capable of being maintained in an undifferentiated state through many passages to be considered embryonic stem cells of the claimed invention. Finally, Appellants argue that the cells must be capable of differentiation into cells from all three germ layers of the early embryo in order to be considered embryonic stem cells of the claimed invention.

These arguments are not persuasive. Appellants have presented no objective evidence to support their position that true ungulate embryonic stem cells share the properties of the cells disclosed in the instant application, and do not have the properties of prior art cells. Appellants have provided no evidence that persons of skill in the art of developmental biology accept the four criteria set out in the Appeal Brief as defining true ungulate embryonic stem cells. "Attorney's argument in a brief cannot take the place of evidence." In re Pearson, 494 F.2d 1399, 1405, 181 USPQ 641, 646 (CCPA 1974).

The record shows only that ungulate embryonic stem cells isolated by the method disclosed in the instant application have the properties alleged in the Appeal Brief to define ungulate embryonic stem cells. That is, the evidence of record is consistent with the cited properties being the result of isolation of the

cells via Appellants' method and not the result of being ungulate embryonic stem cells per se. The record evidence does not support Appellants' conclusion that any cell not sharing the four recited characteristics is not an ungulate embryonic stem cell.

In addition, even if Applicants' properties were accepted as being definitive of ungulate embryonic stem cells, at least one cell line disclosed in the prior art appears to fit the bill. Piedrahita discloses an ungulate embryonic cell line P3. This cell line is disclosed to "survive[] to the tenth and subsequent passages," satisfying Appellants' third criterion. The cell line also gives rise to "round cells with large nuclei and prominent nucleoli[,] . . . resembling mouse teratocarcinoma stem cell colonies." All of these features are shared by Appellants' stem cells, and therefore the P3 cell line appears to satisfy Appellants' first criterion of differing from the morphology of murine embryonic stem cells. Although Piedrahita does not disclose whether the P3 cell line was fast-growing or slow-growing, nor what types of cells the P3 cell line gave rise to, all of the disclosed properties of the P3 cell line are consistent with the P3 cells being ungulate embryonic stem cells, according to Appellants' own definition.

Appellants also argue that later publications by Piedrahita—his Ph.D. thesis and a published research article—show that Piedrahita himself concluded that the cells isolated in the relied-upon reference were not truly embryonic stem cells. Specifically, Appellants argue that Piedrahita noted in his thesis that "the term embryonic stem-like (ES-like) is used to distinguish embryo-derived cells based on morphology; it is not used to imply that the cell line has pluripotential capabilities."[3] Appeal Brief, page 10.

[3] Appellants rely on the Piedrahita thesis and the examiner states that the "Piedrahita Dissertation . . . was carefully considered." Examiner's Answer, page 8. However, the Piedrahita thesis was

This argument is also not persuasive, because the record contains no evidence connecting the definition given by Piedrahita in his thesis with the work described in the relied-on Piedrahita reference. That is, there is no evidence in the record showing that Piedrahita considered the term "embryonic stem cell-like," as used in the relied on reference, to have the definition that was provided in the thesis. Thus, the thesis does not show that the cells in the relied-on Piedrahita reference did not have pluripotential capability.

Appellants' reliance on Piedrahita's later-published research article (referred to as "Piedrahita II" in the Appeal Brief) is also misplaced. Appellants argue that in that article, Piedrahita reported failure to induce differentiation in vitro of porcine embryo-derived cell lines having a morphology similar to mouse ES cells. Appellants' argument fails because, again, there is no evidence in the record to indicate that the cell lines that were reported not to differentiate in the later research article are the same as the cell lines disclosed in the relied-on Piedrahita reference. The later research article does not refer to the cell lines by the designations given in the relied-on reference (P3, G8, etc.). In addition, the relied-on reference does not indicate that the cell lines disclosed therein have "a morphology resembling that of murine ES cells," like the cells that failed to differentiate in the later article. Therefore, the evidence of record does not show that the results reported in the later article apply to the cells disclosed in the relied-on reference.

Finally, Appellants have submitted a declaration under 37 CFR § 1.132 by Martin J. Evans, one of the inventors of the instant application. In his declaration,

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not cited on a Information Disclosure Statement, and we find no copy of the thesis in the file. We find it unnecessary to return the application to the examiner to resolve the issue, however, since even if Appellants' characterization of the thesis is accepted, it fails to show that the rejection is erroneous.

Dr. Evans provides a brief tutorial in mammalian development, a "glossary" of relevant terms, and a table setting out Dr. Evans' interpretation of the published work of others in the field. In particular, Dr. Evans interprets the results disclosed by Piedrahita and concludes that Piedrahita did not isolate embryonic stem cells because "the cells obtained [by Piedrahita] were later shown not to have the capacity of differentiation," citing Piedrahita's Ph.D. thesis as support.

The Evans declaration does not show that the prior art products differed from those of the instant claims. The declaration adds no evidence to what is disclosed in the references in the record. It merely presents Dr. Evans' interpretation of the other references. Dr. Evans' interpretation of Piedrahita's data is based solely on an experimental result allegedly presented in Piedrahita's thesis. However, Dr. Evans does not explain how the data in the Piedrahita thesis led him to conclude that the cells disclosed therein, and allegedly shown to lack the capability to differentiate, are identical to the P3 cell line discussed in the relied-on Piedrahita reference. Therefore, as evidence to show that the P3 cell line disclosed by Piedrahita does not meet the limitations of the instant claims, the Evans declaration carries little, if any, weight.

In conclusion, the evidence of record shows that the cells disclosed by Piedrahita share several characteristics with the ungulate embryonic stem cells described and claimed in the instant application. Among other things, both the prior art cells and the specification's are round cells with large nuclei and prominent nucleoli, which resemble teratocarcinomas. All of these properties indicate that the P3 cells disclosed by Piedrahita were ungulate embryonic stem cells, even by Appellants' definition. The evidence of record therefore supports the examiner's finding that the cells disclosed by Piedrahita anticipate the

instant claims. Appellants have not met their burden of showing that the product in the prior art differs from the product of the instant claims. The rejection under 35 U.S.C. § 102(b) is therefore affirmed.

2. The rejection under § 103

The examiner rejected method claims 8 and 9 over either Ware or Doetschman, in view of Evans. According to the examiner, the method taught by each of Ware and Doetschman meets all the limitations of claims 8 and 9, except that neither of these references discloses the use of a culture medium containing both heat-inactivated newborn calf serum and heat-inactivated fetal calf serum.[4]

The examiner finds this deficiency to be remedied by Evans, who "teaches that it is well-known in the art to use both newborn calf serum and fetal calf serum to supplement [the] growth medium when culturing pluripotential embryonic cells." Examiner's Answer, page 6. Thus, the examiner rejected the claimed method as obvious under 35 U.S.C. § 103.

Appellants argue that the use of heat-inactivated newborn calf serum, together with heat-inactivated fetal calf serum, is a critical limitation of the claimed method. Brief, page 21. Appellants argue that Ware does not disclose use of heat-inactivated newborn calf serum in the ES cell growth medium and

[4] The examiner also acknowledged that neither reference discloses selecting stem cells based on the characteristics recited in claim 8, but "deemed [it] a matter of judicious choice by the skilled artisan to select the stem cells based upon morphological features." Examiner's Answer, page 6. Although Appellants have not argued that this approach was erroneous, we note that claim 8 requires selection based on specific morphological features (round cells, large nuclei, etc.), not morphological features generally. The failure of the prior art to teach or suggest this limitation of the claimed method is an independent basis for reversing the rejection. See In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure." (citations omitted, emphasis added)).

that neither Ware nor Evans teach any advantage associated with using heat-inactivated serum.

"It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." Pro-Mold & Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

> Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious "modification" of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992).

In this case, the claimed method requires use of a growth medium containing both heat-inactivated fetal calf serum (heat-inactivated FCS) and heat-inactivated newborn calf serum (heat-inactivated NCS). Ware teaches a method of growing ungulate embryonic stem cells that includes growing cells in a medium containing heat-inactivated FCS. Evans teaches growth of mouse embryonic stem cells in medium containing both FCS and NCS, but does not teach or suggest that heat-inactivation of the sera is desirable.[5]

Thus, none of the references relied on by the examiner teach the inclusion of heat-inactivated NCS, together with heat-inactivated FCS, in growth medium for ungulate embryonic stem cells. Nor do the references suggest that changing the sera added to the growth medium taught by Ware, specifically by adding

[5] Doetschman is directed to a method of growing hamster embryonic stem cells. The examiner has not explained why a person of ordinary skill in the art would have found the teachings of Doetschman to be relevant to the claimed method of growing ungulate embryonic stem cells. Therefore, we find that the teachings of Doetschman do not support the instant rejection.

heat-inactivated NCS, would be a desirable modification for growing ungulate embryonic stem cells.

In effect, the instant rejection says that it would have been obvious to vary the composition of the growth medium for ungulate embryonic stem cells, even though the prior art gives no indication that inclusion of heat-inactivated NCS was critical and no direction as to what modifications in the growth medium would likely be successful. This is not obviousness under § 103, but rather an "obvious-to-try" rejection, as discussed in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988): "In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." We, therefore, reverse this rejection.

SUMMARY

We affirm the rejection of claims 1-4 and 14 under 35 U.S.C. § 102(b) and reverse the rejection of claims 8 and 9 under 35 U.S.C. § 103.

AFFIRMED-IN-PART, REVERSED-IN-PART

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